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Improved Compaction and Packing Properties of Naproxen Agglomerated Crystals Obtained by Spherical Crystallization Technique

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Naproxen was crystallized from acetone-water in the presence of different concentrations of hydroxypropylcellulose (HPC). Naproxen particles recrystallized in the presence of HPC exhibited an obvious improvement in their packing, flow, and mechanical properties compared to naproxen recrystallized in the absence of the polymer (control particles). The results showed that the particle size distributions of the treated samples were broader than those obtained when HPC was absent. The agglomerates produced in the presence of 0.25% HPC displayed superior flow characteristics (displaying both a low angle of repose and Carr index) in comparison to samples produced in the presence of other concentrations of HPC. This was attributed to the spherical shape and smooth surface, since the area of contact in the powder bed for spherical agglomerates was smaller than that for other crystal shapes. However it was found that the tensile strength of tablets with the particles isolated in the presence of 1% HPC was increased to a greater extent than tablets produced using the spherical particles. Generally, the tensile strengths of the tablets increased with increasing concentrations of HPC present in the crystallization medium. Differential scanning calorimetry (DSC) and X-ray powder diffraction studies showed that naproxen particles, crystallized in the presence of HPC did not undergo structural modifications.

Keywords naproxen; spherical crystallization; HPC; packing and compaction properties

INTRODUCTION

Direct tableting has become the preferred method of tablet manufacture since many processing steps (granulation, drying, etc.) are eliminated and, in addition, wet technology cannot be used to tablet moisture-sensitive agents (e.g., in the manufacture of effervescent tablets) (Shangraw, 1989). However, the use of this technique, although conceptually quite simple, depends on generating appropriate: (a) particle size and particle size distribution of the materials, (b) flowability of the crystals, (c) bulk density of the powder, in order to feed the correct amount of drug into a die cavity, and (d) compactibility of the powder.

Despite some drug crystals exhibiting such appropriate properties, many materials display poor flowability and compactibility (Tanguy & Marchal, 1996). In order that such latter materials may be tabletted, possible solutions could involve: (a) the use of wet granulation, agglomeration (Muller, Seville, & Adams, 1991) (if this is possible with regard to the drug stability), (b) the use of "appropriate" excipients, which can be incorporated by premixing to promote direct tableting (though this might not be favorable in terms of powder flow), (c) the use of direct tableting using spherical agglomerates of drug crystals with good flowability and compactibility properties.

A spherical crystallization technique has already been successfully applied to improve the micromeritics properties of drugs (Kawashima et al., 1994). This technique has been reported to improve the wettability and dissolution rate of different drugs (Di Martino et al., 1999; Guiliaume, Guyot, & Guyot, 1993; Kawashima et al., 1986; Sano et al., 1992).

Recrystallization using a spherical agglomeration technique involving the incorporation of polymeric materials has been found to modify drug release (Akbuga, 1989; Ribardieri, Tchoreloff, Couarraz, & Puisieux, 1996).

Spherical crystallization is defined as an agglomeration technique that directly transforms crystals into a compacted

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spherical form during the crystallization process (Kawashima, Okumura, & Takenaka, 1982). Two main variations of this technique have been applied: spherical agglomeration and quasi-emulsion solvent diffusion; modifications to the processes have been suggested for specific drug formulation purposes (Kawashima et al., 1982, 1989). The habit of microcrystals, as well as crystal growth and agglomeration may be affected by the conditions of spherical crystallization. In addition the presence of polymer added as an emulsifier may affect such parameters.

The aim of the present study was to examine the effects of a single polymer, hydroxypropylcellulose (HPC), on the formation and agglomeration of naproxen microcrystals. Naproxen was selected as a model drug due to its poor flowability and relatively poor compactibility properties. Therefore the objective was to investigate the effect of HPC concentration on the physicomechanical and micromeritics properties of the resulted agglomerated naproxen particles, recrystallized from acetone-water.

EXPERIMENTAL PROCEDURES

Naproxen (Shasun Chemicals, India), HPC (Nisso HPC-H, Nippon Soda, Japan) magnesium stearate (BDH, Poole, England), and acetone (Merck, Germany) were used.

Crystallization Procedure

Naproxen (1 g) was dissolved in 4 mL of acetone at 50°C. This solution was added to 50 mL distilled water (20°C) containing different concentrations of HPC (0.1, 0.25, 0.5, and 1% w/v) under fixed stirring conditions (200 rpm, paddle type agitator with four blades). The precipitated crystals were collected after 10 min by vacuum filtration onto a sintered glass filter. The harvested crystals were evenly spread on an oversized petri dish and were dried for 12 h in an oven (60°C). The dried crystals were stored in screw-capped jars at room temperature before use.

Viscosity Measurements

A Brookfield RVT viscometer was used to measure the viscosities (in cps) of the solution containing various concentration of HPC. A spindle (no. 2) was rotated at 10 rpm and 25°C.

Particle Size Analysis

A total of 25 g of material was sieved using an Erweka vibration sieve (Erweka, Germany) through a nest of sieves. The vibration rate was set at 200 strokes/min and the sieving time was 10 min. The powder fractions retained by the individual sieves were determined and expressed as mass percentages. In the case of the control naproxen, particle size of crystals was measured using the scanning electron micrographs. Each determination was carried out on a minimum of 100 crystals.

Measurement of Packability

The packing ability of the samples was investigated by tapping them into a 25 mL measuring cylinder using a tapping machine (Konishi Seisakusho Co., Japan). Initially, 25 g of substance was weighed and then was gently poured into a measuring cylinder. The volume of 25 g samples was recorded. The poured density (minimum density) was calculated from the powder mass (25 g) and the volume. Then the cylinder was tapped and the volume was recorded after every 100 taps until the volume did not change significantly.

The packability was evaluated by measuring the tapped density according to the modified Kawakita equation (Kawakita & Tsutsumi, 1966):

$$(n / C) = (1 / ab) + (n / a) \tag{1}$$

where, a and b are the constants, n is the tap number, C denotes the volume reduction which can be calculated according to the Eq. (2),

$$C = (V_0 - V_n) / V_0 \tag{2}$$

where, V_0 and V_n are the powder bed volumes at initial and n^{th} tapped state, respectively.

The data were also analyzed by Kuno (Kuno, 1979) equation:

$$\text{Ln}\,(\rho_f - \rho_h) = -kn + \ln(\rho_f - \rho_0) \tag{3}$$

where, ρ_f, ρ_n, and ρ_0 are the apparent densities at equilibrium, n^{th} tapped and initial state, respectively, and k is a constant.

The packing ability was assessed by comparing the constants a, b, and k in Eqs. (1) and (3), respectively. The constant a represents the proportion of consolidation at the closest packing attained. The apparent packing velocity obtained by tapping is represented by parameter b. The constant k in Kuno's equation represents the rate of packing process.

Scanning Electron Microscopy (SEM)

The morphology of crystals (their habits and surface features) was examined using a scanning electron microscope (LEO 440I, Cambridge) operating at 15 kV. The samples were sputter-coated with gold before examination.

X-Ray Diffraction of Powder (XRDP)

A Seimens (Model D5000, Germany) X-ray diffractometer was used at 40 kV, 30 mA and a scanning rate of 0.06° min^{-1} over a range of 2–40 2θ, using $CuK_{\alpha 1}$ radiation of wavelength 1.5405 Å.

Differential Scanning Calorimeter (DSC)

Samples of naproxen crystals (5 mg) were heated (ranging from 25–200°C) at 5°C min^{-1} in hermetically sealed aluminum

pans. The melting point and onset temperatures were automatically calculated (DSC60, Shimadzu, Japan).

Measurement of Flowability

Flowability of the crystals was assessed by determining the compressibility index (Carr index) and the angle of repose. The Carr index (Carr, 1965) is a measure of the propensity of a powder to consolidate. The preliminary results showed that after 1250 taps the volume change was negligible for all the samples. So, the samples were taped 1250 times in this experiment. Changes occurring in packing arrangement during the tapping procedure are expressed as the Carr index (Eq. (4)).

$$\text{Carr index } (\%) = [(\rho_t - \rho_b)/\rho_t] \times 100 \quad (4)$$

where, ρ_t and ρ_b are tap density and bulk densities of powder bed, respectively.

The Carr index reflects the compressibility of the powders, and there is a correlation between the compressibility index and the flowability of the crystals.

The angle of repose was measured by a fixed funnel method. The results presented are mean value of six determinations.

Preparation of Compacts

The agglomerates and the control crystals were directly compacted using 8 mm flat-faced punches on a hydraulic press (Riken Seiki Co, Japan). The material for each tablet was weighed (200 mg), introduced into the die and compacted at various compaction pressures of 5, 10, 15, 20, and 25 MPa. The compaction surfaces were lubricated with 1% w/w magnesium stearate in ethanol before compaction. The compacts were held under load for 30 sec, ejected, and stored in screw-capped bottles for 24 h before using, to allow for possible hardening and elastic recovery.

Tablet Tensile Strength

The force required to fracture the compacts on a motorized tablet hardness tester (Erweka, Germany) was measured (F). The tensile strength (T) of the compacts was calculated based on the Eq. (5) (Fell & Newton, 1970; Rundick, Hunter, & Holden, 1963)

$$T = 2F/(\pi Dt) \quad (5)$$

where, D and t are the diameter and thickness of the compact, respectively. The results are the mean of five determinations.

Determination of Drug Content in Agglomerates

A weighed quantity of agglomerates was triturated and dissolved in ethanol by sonication. The solution was filtered and after sufficient dilution with ethanol analyzed spectrophotometrically at 330 nm (UV-160, Shimadzu, Japan). Drug content was calculated from the calibration curve of naproxen in ethanol. The means of 3 assays were reported.

RESULTS AND DISCUSSION

Effective use of the spherical crystallization procedure involves a quasi-saturated solution of the drug, in a solvent in which it is very soluble, being poured into an anti-solvent for the drug. Provided that the good and anti-solvents are freely miscible and interaction (binding force) between the solvents is stronger than the drug interaction with the good solvent, crystals precipitate immediately. In this study, the crystallization of naproxen from the solvent aceton was performed by the addition of a solution to the anti-solvent phase (water) containing different concentration of HPC. The presence of different concentrations of HPC is likely to modify the interfacial tension between the transiently dispersed solvent and continuous phase and the drug solution after dispersion in the poor solvent produces quasi-emulsion droplets, due to a measurable interfacial tension being established between the good and poor solvent. The acetone then diffuses gradually out of the emulsion droplet into the outer anti-solvent phase (water). The counter-diffusion of the anti-solvent into the droplet induces the crystallization of the drug within the droplet due to the decreasing solubility of the drug in the droplets containing the poor solvent.

It is apparent from the scanning electron micrographs (SEMs) that the addition of HPC to the crystallization medium considerably affected the crystal shapes of naproxen (Figures 1–6). The control naproxen particles were plate-shaped crystals, whereas naproxen crystallized from acetone in the presence of HPC had an agglomerated structure consisting of numerous plate-shaped crystals which had struck together.

The particles obtained in the presence of 0.1 or 0.25% HPC in the crystallization medium were spherical in shape (most notably those samples recrystallized in the presence of 0.25% HPC). However, as the concentration of HPC was increased from 0.25 to 1% w/v in the crystallization medium, the resultant

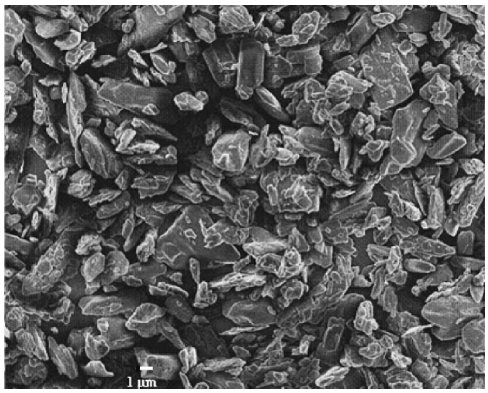

FIGURE 1. SEM photomicrographs of the control naproxen crystals.

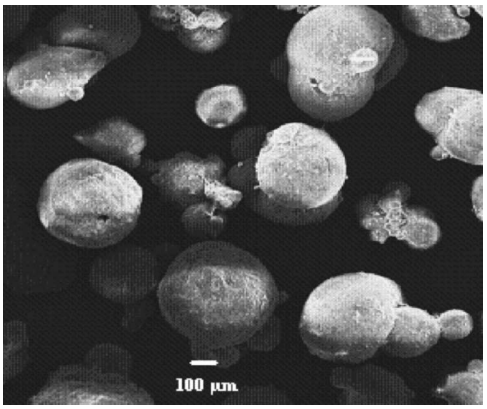

FIGURE 2. SEM photomicrographs of naproxen particles recrystallized in presence of 0.1% HPC.

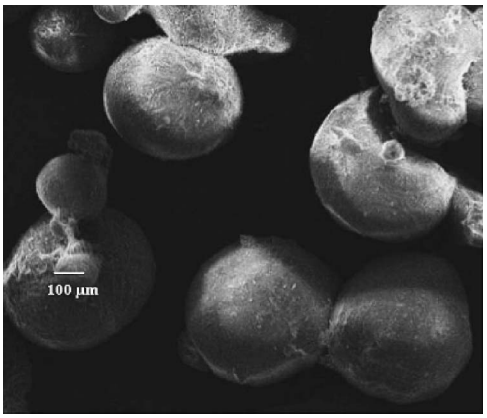

FIGURE 3. SEM photomicrographs of naproxen particles recrystallized in presence of 0.25% HPC.

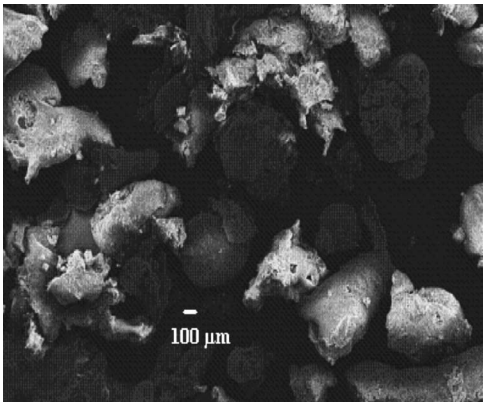

FIGURE 4. SEM photomicrographs of naproxen particles recrystallized in presence of 0.5% HPC.

particle shape departed from the spherical to irregular agglomerated particles (Figures 4 and 5). These findings can be explained as follows. Solubility of HPC in acetone is lower

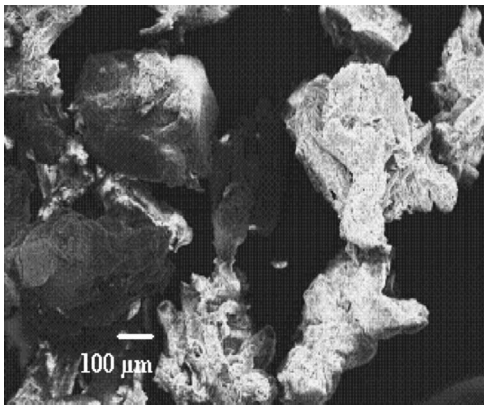

FIGURE 5. SEM photomicrographs of naproxen particles recrystallized in presence of 1% HPC.

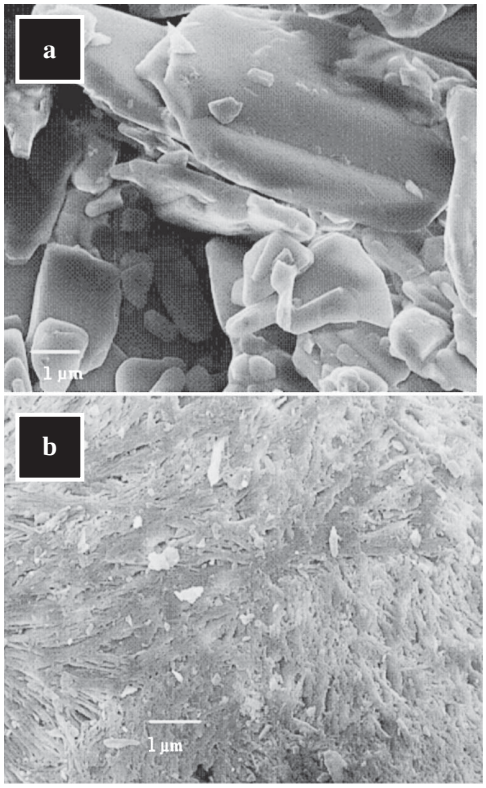

FIGURE 6. SEM photomicrographs of surface of (a) the control naproxen and (b) treated particles in presence of 0.25% HPC.

than in water, therefore, HPC in the crystallization medium tends to precipitate by phase separation with acetone. The amount of precipitated HPC might affect the shape of the particles crystallized in the presence of 0.5 and 1% HPC. However, at lower concentration of HPC the amounts of precipitate are probably too small to affect the morphology of the particles.

An examination of the SEMs shows that the control material was markedly smaller than any of the particles obtained from

acetone-water solution in the presence of HPC, which is due to crystals agglomeration in these particles. The particle size distributions of the agglomerates were broader than the size distribution of the control sample. As seen in Figure 7, the majority of the agglomerates were between 500–710 μm, whereas the diameter of majority of the particles comprising the control material was distributed between 2–5 μm. The mean diameters of the agglomerated particles were approximately 50 times higher than those of the control crystals (Table 1).

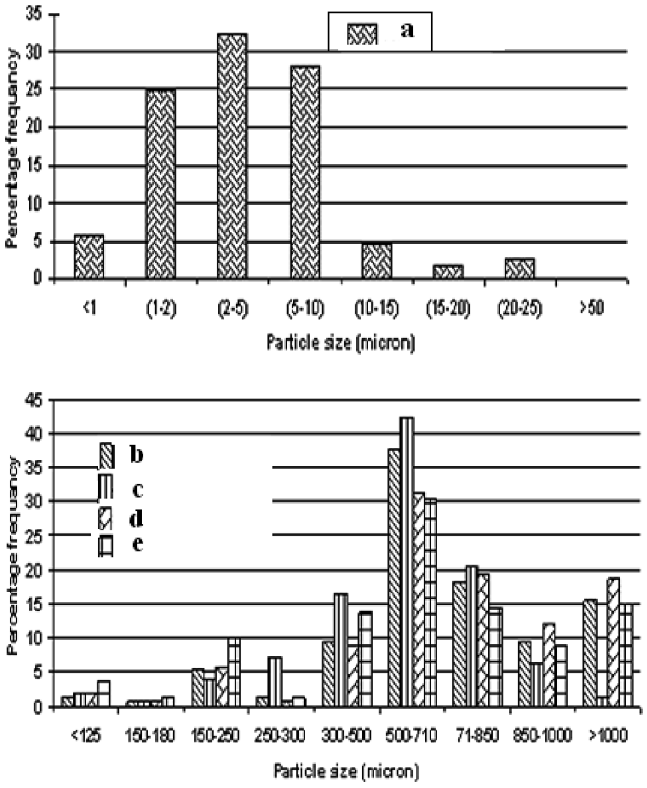

FIGURE 7. Particle size distribution of (a) the control naproxen crystals and naproxen recrystallized in the prescence of (b) 0.1% HPC, (c) 0.25% HPC, (d) 0.5% HPC and (e) 1% HPC.

Table 1 summarizes the micromeritics data obtained for the various samples. The Carr index and angle of repose revealed that the flowability of the control product was very poor (Table 1). The naproxen powder produced in the presence of 0.25% HPC exhibited the best flowability (exhibiting the lowest angle of repose and Carr index). This is attributable to spherical shape of the particles (Figure 3), since the area of contacts in the powder bed for spherical agglomerates was smaller than that for other particle shapes.

Table 2 summarizes the packability parameters data obtained for the various samples via the modified Kawakita and Kuno equations (Eqs. (1) and (3)).

The low values of the Carr index and parameter a of the Kawakita equation for the agglomerates indicated that the agglomerated crystals have better packability. In other words they are well packed before tapping since tapping does not improve the packing significantly, it only reorganizes the agglomerated particles presumably without changing their shape and size significantly. The apparent packing velocity obtained by tapping, represented by parameter b, for the agglomerates was slower than that for the control particles, since the agglomerates were packed more closely, even without any tapping, as a consequence of their better flowability and packability. The larger k (derived from Eq. (3)) obtained for the agglomerates confirmed these findings. The main reasons for better packability of the agglomerated particles and less packability of the control particles might be due to the difference in particle size distribution and particle shape. The packing of the agglomerates with wider particle size distribution (Figure 7) is indeed expected to be higher than that of the control particles.

Agglomerates were spherical in shape compared with the control crystals, thus good packability of agglomerates was also attributed to the spherical shape, since the area of contacts in the powder bed for the agglomerates was smaller than that for plate-shaped control particles.

The improved flow properties and packing ability of the agglomerated crystals would indicate that they might be suitable for direct tableting. In spite of better packability of the

TABLE 1
Micromeritics Properties of the Control Powder and the Modified Crystals Obtained in the Presence of Different Concentrations of HPC (n = 5)

Materials	Arithmetic Mean Diameter (μm)	Angle of Repose (°)	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Carr Index (%)
The control	9.05	62.66 ± 0.66	0.373 ± 0.004	0.588 ± 0.007	36.56 ± 1
Treated with:					
0.1% HPC	515.2	45.9 ± 0.97	0.270 ± 0.001	0.324 ± 0.001	16.67 ± 0.6
0.25% HPC	574.3	39.3 ± 0.40	0.215 ± 0.004	0.238 ± 0.001	9.66 ± 0.5
0.5% HPC	506.9	45.9 ± 0.84	0.175 ± 0.002	0.207 ± 0.001	15.45 ± 0.8
1% HPC	468.0	46.3 ± 0.63	0.167 ± 0.001	0.206 ± 0.001	18.90 ± 0.9

TABLE 2
Packability Parameters of the Control Naproxen and Samples Crystallized in the Presence of Different Concentrations of HPC

Materials	a[a]	b[a]	k[b]
The control naproxen	0.373 (r = 0.999)	0.080	0.0035 (r = 0.994)
Treated with 0.1% HPC	0.176 (r = 0.992)	0.029	0.0075 (r = 0.997)
Treated with 0.25% HPC	0.098 (r = 0.998)	0.017	0.0050 (r = 0.999)
Treated with 0.5% HPC	0.168 (r = 0.999)	0.010	0.0042 (r = 0.998)
Treated with 1% HPC	0.202 (r = 0.997)	0.020	0.0044 (r = 0.992)

[a]Parameters in Eq. (1), [b]Parameter in Eq. (3), and r, correlation coefficient.

agglomerates, the bulk and tapped densities of the agglomerates are lower than that of the control sample (Table 1). In fact, the only way to have better packing and lower bulk density is to have less dense particles and hence porous particles. The results of SEM supported this conclusion. SEMs of the control naproxen and samples crystallized in the presence of HPC with high magnification (Figure 6) revealed that there was no evidence of porosity in the control naproxen whereas the agglomerated particles showed clear evidence of being porous.

An increase in the concentration of HPC in the crystallization medium resulted in a reduction in the bulk and tap densities of the particles. This could be related to the higher viscosities of the medium containing higher amounts of HPC. It has been shown that an increase in solution viscosity reduces the crystal growth rate (Mackellar et al., 1994). In order to describe the effect of HPC on the physical properties of the treated particles, the viscosity of the HPC solutions at various concentrations was measured and the results are shown in Table 4. As the concentration of HPC increases the apparent viscosity of medium increases, thus the rate of crystal growth may decrease as a function of HPC concentration within the continuous phase. On the other hand, with increasing concentration of HPC, the induction time (the time taken for appearance of the first visible particles) increased, which may be attributed to the adsorption of HPC onto the crystal surfaces. It has been shown that the longer time for formation of agglomerates led to less dense agglomerates (Paradkar, Pawar, Chordiya, Patil, & Ketkaar, 2002). As a result, the differences in densities of the agglomerates are likely to be related to the different particle density. On the other hand, different crystal habits, different particle sizes, and different surface roughness affect the sliding of the particles against each other, leading to differences in packing geometry and bulk density (Kachrimanis, Ktistis, & Malamataris, 1998).

X-ray powder diffraction pattern (XRPD) in the 10–40 2θ range showed that the diffraction peaks of naproxen were still detectable in the crystallized samples (Figure 8), suggesting that particles crystallized in the presence of HPC did not undergo structural modifications. However, the differences in the relative intensities of their peaks may be attributed to differences in the crystal sizes, habits, and crystallinity of the samples (El-Said, 1995; Jbiilou, Ettabia, Gguyot-Hermann, & Guyot, 1999; Marshall & York, 1989).

The uniformity of crystalline structure in all batches was confirmed by DSC, where the use of HPC in the crystallization of naproxen was shown to have no effect on the melting point of the drug, irrespective of polymer concentration (Table 3). All samples showed a sharp melting point with flat baseline, which indicated that the material had not been affected by hydration, solvation, and no polymorphic transition had occurred during crystallization of the particles (Figure 9).

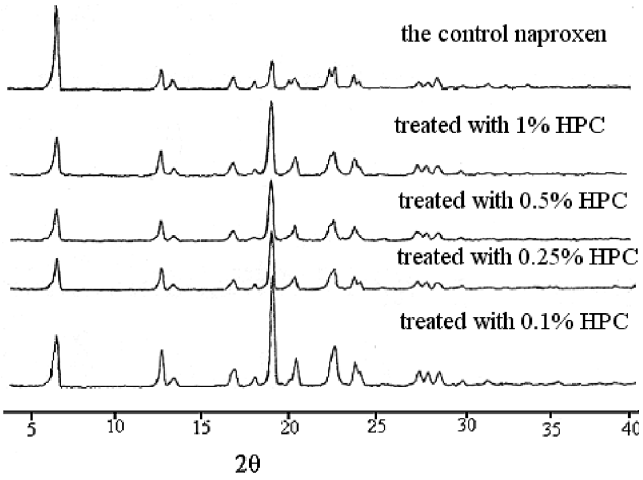

FIGURE 8. The X-ray diffraction spectra of the control naproxen and recrystallized naproxen in presence of different concentrations of HPC.

TABLE 3
Melting Point Onset, Melting Peak Temperatures for the Control Naproxen and Naproxen Crystallized in the Presence of Different Concentrations of HPC (the Results are the Mean and Standard Deviation of at least 5 Determinations)

Materials	Melting Point Onset (°C)	Melting Peak (°C)
The control naproxen	153.81 ± 0.29	157.31 ± 0.10
Treated with:		
0.1% HPC	153.44 ± 0.78	157.06 ± 0.17
0.25% HPC	153.28 ± 0.49	157.0 ± 0.23
0.5% HPC	153.28 ± 0.16	157.28 ± 0.27
1% HPC	153.05 ± 0.34	156.98 ± 0.07

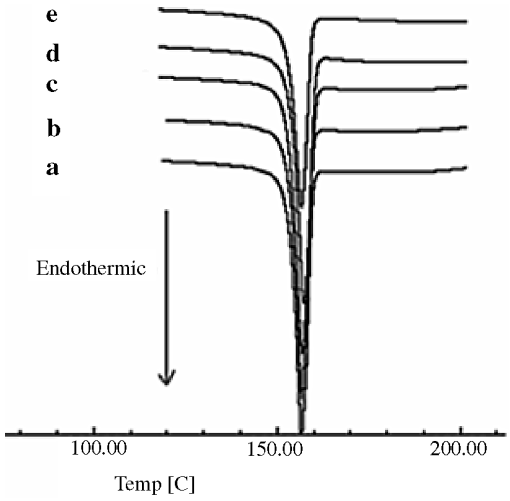

FIGURE 9. DSC scan of (a) the control naproxen crystals and naproxen recrystallized in the prescence of (b) 0.1% HPC, (c) 0.25% HPC, (d) 0.5% HPC and (e) 1% HPC.

Good compactibility is also the essential property of directly compactible crystals. The influence of compaction pressure on the tensile strength of tablets made from naproxen particles crystallized in the presence of different concentration of HPC is shown in Figure 10. The agglomerated crystals, obtained by crystallization in the presence of various concentrations of HPC, possessed superior tensile strength characteristics in comparison to the control crystals. The high tensile strengths of the tablets are indicative of stronger interparticulate bonding between the particles crystallized in the presence of HPC compared to the control naproxen.

The improved compactibility of the agglomerates was attributed to their structural characteristics. Agglomerates were comprised of small crystals, as shown in Figure 6b and this characteristic structure were responsible for the large relative volume change, which occurred during the early stage of the compaction process, as a consequence of fragmentation of the particles. It has been shown that a reduction in bulk density results in an increase in the tensile strength of tablets (Zuurman, Riepma, Bolhuis, Vromans, & Lerk, 1994). A comparison of the tensile strengths of the tablets (Figure 10) with bulk density data (Table 1) indicated that similar results were obtained in this study. Generally, the tensile strengths of the tablets increased with increasing the concentration of the HPC present in the crystallization medium.

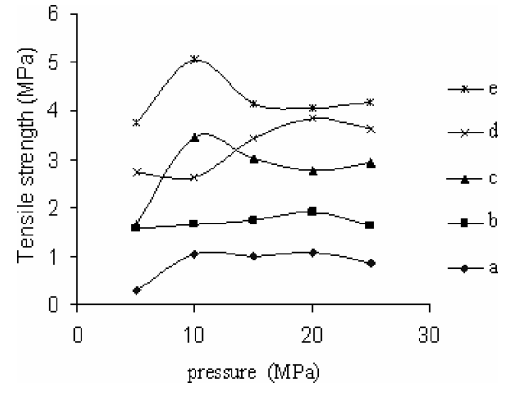

FIGURE 10. The tensile strengths of the tablets made from (a) the control naproxen crystals and naproxen recrystallized in the prescence of (b) 0.1% HPC, (c) 0.25% HPC, (d) 0.5% HPC and (e) 1% HPC.

Table 4 shows that increasing the concentration of HPC in the crystallization medium results in reduced drug content in the agglomerates. This is clearly due to an increase in the amount of HPC adsorbed by the particles. It is thought that the improvement in the compaction properties of naproxen agglomerates upon increasing the concentration of HPC in crystallization medium could be explained by the reduction of bulk density, as well as the higher amounts of the adsorbed HPC acting as a binder. Nystrom and Glazer (1985) found that the tablet strength of physical mixtures of a poorly compactible substance, such as paracetamol with binders such as, polyvinylpyrrolidone, increased with an increase in the concentration of binder.

Lubricants are commonly included in tablet formulations in order to reduce die wall friction during both compaction and ejection of the tablet but their inclusion can lead to undesirable changes in tablet properties, such as a reduction in tablet strength. It is possible to compare the lubricant sensitivity using Eq. (6) where lubricant sensitivity ratio (LSR) can be derived as a quantitative measure to express the sensitivity of the tablet to incorporated lubricants. The LSR is the ratio between the decrease in crushing strength of tablets, due to mixing with a lubricant and the crushing strength of unlubricated tablets:

$$LSR = (Cs_u - Cs_l)/(Cs_u) \quad (6)$$

where, Cs_u and Cs_l are the crushing strengths of tablets prepared without and with a lubricant, respectively.

TABLE 4
Drug Content of the Agglomerates and Viscosity of HPC Solution at Different Concentrations

Concentration of HPC in the Crystallization Medium (% w/v)	Viscosity of HPC Solution (cp)	Amount of Drug in Agglomerates (%)
0.1	68.6	99.18 ± 0.33
0.25	175.8	98.5 ± 0.40
0.5	586.3	97.32 ± 0.55
1	2455.2	94.47 ± 0.62

TABLE 5
The Susceptibility of Naproxen Tablets, Prepared from the Control Drug or Drug Crystallized in Presence of Different Concentrations of HPC to the Incorporation of 2% w/w Magnesium Stearate (Compression Force was 20 Mpa, $n = 5$)

Materials	Cs_u (kgf)	Cs_l (kgf)	LSR
The control naproxen	10.48 ± 1.04	7.30 ± 1.27	0.30
Treated with:			
0.1% HPC	18.42 ± 1.25	17.64 ± 1.88	0.04
0.25% HPC	25.38 ± 2.96	17.66 ± 2.53	0.30
0.5% HPC	30.66 ± 4.20	25.66 ± 1.93	0.16
1% HPC	39.12 ± 0.76	26.98 ± 4.81	0.30

The effect of the addition of magnesium stearate (2% w/w) on the crushing strength of naproxen tablets is shown in Table 5. An almost 30% drop in crushing strength of the control naproxen tablets occurred when magnesium stearate was added to the control naproxen powder. When magnesium stearate was added to naproxen crystals recrystallized in the presence of 0.1% HPC or 0.5% HPC, there was a 4% or 16% reduction in crushing strength of the tablets. However samples recrystallized in the presence of 0.25 or 1% HPC showed a 30% reduction in crushing strength.

Magnesium stearate has been found to decrease mechanical strength in many tablets studied especially those formed from crystals (Shotton & Lewis, 1964). It is thought that it acts as a physical barrier forming a coat around individual particles, interfering with bonding properties. The nature of surface coverage is thought to vary between adsorption leading to surface coverage, solid penetration including mechanical interlocking and deagglomeration of the lubricant particle to form a film coating on the particles (Shah & Mlodozeniec, 1977). In order for a lubricant to have effect on a powder there must be good distribution of the lubricant, i.e., the powder must have good flow properties. Otherwise these processes would be slow and less likely to occur. The degree of influence of a lubricant on compaction behavior of a powder has been attributed to the bonding and compaction mechanism of the material (DeBoer, Bolhuis, & Lerk, 1978). Bonding of brittle materials is not influenced by lubricant because clean, lubricant-free surfaces are created by fragmentation of the particles during consolidation of the particle system. In contrast, the lubricant has maximum effect when combined with a material that undergoes plastic deformation without fragmentation, under compaction, and is bonded by cohesion. It is probable that the formulations developed in this study will fall somewhere between these two extremes. The overall effect of lubricant will depend on the extent of fracture of particles during compaction.

CONCLUSION

Spherically agglomerated crystals of naproxen were successfully prepared using the spherical crystallization technique. The micromeritic properties of the agglomerates such as flowability, packability, and compactibility were dramatically improved, resulting in successful direct tableting without capping.

This study showed that the samples crystallized in presence of 0.25% HPC had excellent flow characteristics. Samples recrystallized in presence of 1% HPC had excellent potential for direct compaction, on the basis of hardness data. There are many active agents in the pharmaceutical industry with unfavorable flowability and compactibility properties (paracetamol, ibuprofen, phenybutazone being well-known examples) and the methods employed in this study may provide an opportunity to create a viable formulation approach.

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